Annals of Clinical & Analytical Medicine
Review

Therapeutic approaches for COVID 19: Challenges and successes

Rim M. Harfouch[1], Samer Alshaikh[2], Mohammad Alshimaly[3], Amany Assaad[3], Jehan Ahmad[3], Haya Zoughaibi[2], Maher Hammadi[3], Yahya Elshimali[4]
[1]Faculty of pharmacy, Al Sham private university, Latakia, Syria
[2]Faculty of medicine, Tartous university, Tartous, Syria [3]Faculty of pharmacy, Tartous university, Tartous, Syria
[4]Faculty of medicine, Charles Drew University for Medicine and Science/University of California Los Angeles (UCLA). USA

Abstract

The novel coronavirus SARS-COV-2 or COVID-19 was first discovered in Wuhan, China in late December 2019 and soon became a global pandemic. The virus causes flu- like symptoms and is potentially lethal. The rapid spread of the virus leaves the world in total paralysis and has devastating effects on the health, economic, and social levels of most countries.

No treatment has been approved yet and the world really needs a precise and urgent medication. Certainly, the developing of a new specific drug for COVID-19 would take a longer time than expected but it is hoped that this task will be completed sooner than later; therefore recent studies have prioritized testing previously FDA-approved drugs for other indications and whether they have significant effects on COVID-19 or not. In this study, we discuss recent applications, protocols, and the outcomes of these drugs as advised by healthcare institutions and providers, as well as to conduct a literature review.

Keywords

COVID-19; Available treatments; Practical approach

DOI: 10.4328/ACAM.20270 Received: 2020-07-02 Accepted: 2020-08-11 Published Online: 2020-08-16 Printed: 2021-02-01 Ann Clin Anal Med 2021;12(2):228-233
Corresponding Author: Rim Harfouch, Department of microbiology and biochemistry, Faculty of pharmacy, Al Sham private university, Latakia, Syria 00000
E-mail: r.h.foph@aspu.edu.sy P: 00963932292303
Corresponding Author ORCID ID: https://orcid.org/0000-0001-7002-8728

Introduction

The novel coronavirus SARS-COV-2 or COVID-19 was first found in Wuhan, China and is the cause of severe acute respiratory distress syndrome [1]. Afterwards, this virus spread rapidly and became a global pandemic. Although the fatality rate is low (reported to be 2.5% as of 12 February 2020) [2], the accelerating transmission makes it a threat to mankind, and finding a curative treatment is a top priority. While no such treatment has been confirmed, many drugs and combinations are being suggested and some have even shown positive clinical results. On January 23, 2020, the first clinical trial for COVID-19 was registered, the number of trials then ascended to reach 125 registered trials by February 18, 2020. The 125 trials utilized various mechanisms of action, 33.3% used anti-viral drugs, 33.3% used traditional Chinese medicine (TCM) and herbs, 14.7% used using anti-inflammatories or immunomodulators, 9.3% used therapies based on cells, 2.3% used antioxidant agents, and 7.0% used other methods [3]. This article is an attempt to summarize the current situation regarding suggested methods of treatment and highlight the progress made towards a trusted treatment.

The mechanism of viral infection and potential therapies:

There are two proteins involved in viral penetration of cells, Angiotensin-Converting Enzyme II (ACE2) and Trans-membrane protease, serine 2 (TMPRSS2).

Angiotensin-Converting Enzyme II (ACE2) receptors are found mainly in the tissue of the lung, but also to a lesser degree in the tissues of the heart, kidney, pancreas, endothelium, and intestine [4]. They protect from lung injury [5], and appear to be the main entry point of the novel coronavirus SARS-COV-2 [6].

The SARS-COV virus binds to ACE2 receptors using its spike (S) protein [7]. It was found that the S protein in SARS-COV-2 is highly similar and also uses ACE2 receptors as entry points. [8] When the S protein binds to Angiotensin II type 1 (AT1) receptors, it results in over-activation of the ACE-AngII-AT1 pathway which has shown to induce inflammatory responses and possibly fibrosis of the lungs or other organs [9].

The logical approach to the therapy is to combat this interaction, thus the S protein presents a prime target for potential vaccines [10]. An article published on 17 March 2020 suggested the use of Losartan (ACE2 antagonist) as a potential protective barrier against the lung damage generated by COVID-19 infection [9]. Another suggested therapeutic option is to provide a soluble form of ACE2 as a competitive interceptor [11]. In a recent study, such a protein was generated by combining the extracellular domain of human ACE2 with the FC region of human immunoglobulin IgG1. The resulting protein had a high affinity for the receptor-binding domain of the virus and potently neutralized SARS-COV-2 in vitro by inhibiting its S protein [12].

SARS-COV-2 also uses the cellular protease TMPRSS2 for cell entry [6] which provides another possible target for therapy. Camostat mesylate is a clinically proven protease inhibitor and a recent study tested its effects on SARS-COV-2, SARS-COV, and MERS-COV where it effectively inhibited the viral infection by inhibiting (TMPRSS2) [13].

The viral entry into the endosomes is also assisted by Cathepsin L, an enzyme involved in innate immunity [14,15]. Cathepsin L has a vital role in viral infections [16]. The virus uses Cathepsin L to remove its S protein from the cell, enabling it to release RNA into the host [15]. Tiecoplanin is a glycopeptide antibiotic and an accustomed treatment for various bacterial infections. It acts on the previous interaction by inhibiting Cathepsin L preventing RNA release and thus the replication of the virus. Teicoplanin was found to inhibit the infection with novel coronavirus COVID-19 and was tested with IC50 = 1.66μM, where it prevented 2019-nCoV-Spike-pseudoviruses from entering the cytoplasm in in-vitro studies [17].

Chloroquine and its derivatives, a promising approach to treatment:

The fact of the S protein affinity to the ACE2 receptors also led to the examination of Chloroquine (CQ), which is an aminoquinoline and is the drug of choice for prophylaxis and treatment of malaria and connective tissue autoimmune diseases unresponsive to other agents [18]. CQ can be used to treat patients infected with the novel coronavirus SARS-COV-2 because it inhibits the glycosylation of ACE2 receptors, and also has alkaline properties which elevate the pH of acidic intracellular organelles, such as endosomes/ lysosomes, essential for membrane viral fusion [19]. However, while CQ itself showed antiviral effects on COVID-19, high dose intake for excessive periods of time induced several side effects [20]. Therefore, Hydroxychloroquine (HCQ) was suggested instead of CQ due to its similar effects as it is safer and causes fewer side effects [20, 21]. It also can be given at a better dosage, as CQ can only be given at a 500 mg dosage, whereas HCQ has a maximum tolerable dosage of 1200 mg, which is as effective as a 750 mg dosage of CQ [21,22].

HCQ proved to be more potent than CQ in vitro [23] and, more notably, a trial in France was published on 20 March 2020 yielding exceptional clinical results by using HCQ in combination with Azithromycin, although this method has a potential risk of severe QT prolongation that should be considered [24]. In China, Chloroquine Phosphate has also been tested on more than 100 patients where it promoted a virus-negative conversion and inhibited the aggravation of pneumonia, which improved lung findings, thus shortening the disease course. Furthermore, no severe adverse effects were noted [25].

On March 29, 2020, the US Food and Drugs Administration (FDA) has granted the emergency use authorization (EUA) for these drugs in the treatment of COVID-19 for a limited number of hospitalized cases, and to better evaluate the effectiveness of these drugs, high-quality randomized clinical trials are required. On the other hand, there are concerns about dangerous heart-related adverse events such as QT interval prolongation, ventricular tachycardia, and ventricular fibrillation in COVID-19 patients treated with hydroxychloroquine and chloroquine alone or in combination with azithromycin according to the American Association of Poison Control Centers National Poison Data System.

Remdesivir:

Remdesivir is an analog of adenosine. Its mechanism of action is to integrate with the chains of nascent viral RNA, causing

premature termination of them. Wang et al. reported that the mechanism of action of remdesivir depends on blocking SARS-CoV-2 infection at low concentrations with a high selectivity index [26].

Although remdesivir (GS-5734) still needs clinical studies to prove its efficiency against COVID-19 but according to its broad-spectrum properties, it is expected to inhibit COVID-19 as it was a potential antiviral drug to treat other CoVs infections [27].

On the 5th of February, 2020, clinical studies on remdesivir in China were started using randomized placebo-controlled, double-blind, multicenter clinical trial. The group of patients included in this study received a primary dose of 200 mg of remdesivir IV then they received a subsequent dose of 100 mg IV for 9 sequential days, while another group of patients received routine treatment with the same dose of placebo [28]. It was used to successfully treat the first American case of SARS-COV-2 [29].

Other antivirals, such as lopinavir/ritonavir, have shown good clinical results against COVID-19 [30].

The number of trials reached 125 registered trials by February 18, 2020, and 33.3% of these trials utilized anti-viral drugs. A combination of remdesivir and chloroquine proved efficiency in inhibiting the recently emerged SARS-CoV-2 in vitro [31].

Several recent trials showed that remdesivir was not associated with clear clinical improvement and the SARS-COV2 presence in the bloodstream was not reduced. Further studies are required to confirm the feasibility and efficacy of using remdesivir for the treatment of COVID-19 patients.

Vitamin C:

Vitamin C is not synthesizable by humans, so it is gained from dietary sources. It is a primary antioxidant and enzymatic cofactor in physiological reactions, which is involved in collagen synthesis, production of hormones, and supports the immune system [32].

When used in an appropriate dose, Vitamin C acts as a powerful antiviral. It can be used alone or combined with other drugs. For many people, frequent oral intake of vitamin C to reach the daily limit of bowel tolerance provides good antiviral effects. Intravenous vitamin C is usually given in critical cases, and the sicker a person is, the more ascorbic acid he would tolerate orally without causing diarrhea. It could be combined with oral multivitamins which is an effective way to prevent coronavirus [33].

Vitamin C in high dosage is considered as rescue therapy in emergency cases [34]. But on the other hand, high doses of vitamin C may have side effects like osmotic death of immune cells, which might create a local inflammation in the alveolar medium; therefore, IV glucocorticoid is combined with vitamin C treatment to reduce the possible inflammatory complications caused by high doses.

Many studies showed that vitamin C might be preventive for the infection of the lower respiratory tract in certain conditions. As COVID-19 may infect the lower respiratory tract, a moderate dose of vitamin C might help in preventing COVID-19 [35].

Lidocaine:

The human-to-human viral spread is mostly caused by coughing, which is one of the common features of COVID-19 infections. Premedication with opioids like fentanyl is usually followed by coughing, therefore, a single IV dose of Lidocaine is given to patients to prevent such features.

Patients with COVID-19 should be administered injections of lidocaine before and after any procedure that requires intubation or/and extubation to prevent coughing [36]

Small Molecules Agents:

One of the strategies currently under study to treat SARS-COV-2 is the combination of small molecules that have anti-inflammatory properties and antiviral drugs. Some of the suggested such drugs are Baricitinib, Fedratinib, and Ruxolitinib, which are strong and selective Janus Kinase (JAK) inhibitors, making them powerful and effective against the consequences of the elevated levels of cytokines (including interferon-γ) typically observed with COVID-19 patients·[37]. These drugs inhibit clathrin-mediated endocytosis which in turn inhibits the viral cellular infection. They also inhibit members of the numb associated kinase (NAK) family including the Adaptor-associated protein kinase (AAK1) and the cyclin G-associated kinase (GAK) which has shown to reduce the viral infection in vitro [39, 40]. Among these drugs, Baricitinib is preferable because it has a particularly high affinity to AAK1[37]. Baricitinib has anti-inflammatory properties and can ameliorate the associated chronic inflammation in interferonopathies [41].

Its side effects and dosage are acceptable (given orally once daily), making it a good choice for treating COVID-19 patients. In addition, this medication has a little affinity to plasma proteins and a poor interaction with cytochrome enzymes making it safe when taken with other drugs, such as directed antivirals (lopinavir or ritonavir and remdesivir) which are currently being used against COVID-19 [38]. The combination of baricitinib and directed antivirals can reduce the viral infection and the inflammatory response [42].

Ivermectin:

Ivermectin is an FDA-approved anti-parasitic [43] with a safe clinical profile [44] which has shown antiviral capacities against a wide spectrum of RNA viruses [45].

Ivermectin was tested against SARS-CoV-2 in vitro where it effectively inhibited the virus, possibly by inhibiting IMPa/b1-mediated nuclear import of viral proteins. Caly et al. found a 93% reduction in viral RNA in the supernatant (the released virions) and a 99.8% reduction in cell-associated viral RNA (unreleased and unpackaged virions) after 24 hours of ivermectin treatment of SARS-CoV-2 infected cells [46]. Clinical evidence and further trials are necessary to confirm Ivermectin as a therapy for COVID-19.

Tocilizumab:

Tocilizumab is a monoclonal antibody against interleukin 6 (IL6) which is used primarily in rheumatoid arthritis. It may confer clinical benefit in COVID19 patients who present with high levels of IL6 [47].

In some critical patients, COVID19 may trigger a cytokine storm

that is associated with high levels of plasma interleukin (IL)-6 as well. Tocilizumab binds to sIL-6R and inhibits the interaction between IL-6 and sIL-6R, thus it prevents the inflammatory response and the respiratory distress [48, 49].

A clinical test was conducted in the First Affiliated Hospital of the University of Science and Technology of China successfully. Twenty patients underwent treatment, and after the first day, the body temperature returned to normal in all of them and the symptoms were greatly relieved. Of the 20 patients, 19 were eventually discharged [50]. The number of patients was too small to draw a conclusion, but these results are promising.

In a clinical study for a series of patients with COVID-19 pneumonia, tocilizumab was administered subcutaneously for the first time, and it revealed good clinical and radiological outcomes [51].

On the other hand, tocilizumab revealed favourable clinical course and a positive impact on survival when used early during Covid-19 pneumonia with severe respiratory syndrome [52].

Ritonavir/Lopinavir, Darunavir, and Danoprevir:

The proteases of the hepatitis C virus (HCV) and the human immunodeficiency virus (HIV) have shown a highly similar function to those of SARS-COV-2 [53], therefore protease inhibitors may have therapeutic effects on the novel coronavirus. Ritonavir and lopinavir, a combination of drugs used to combat HIV [54], are antivirals that bind to the protease-like domain CEP-C30 on SARS-COV and SARS-COV-2 [55]. They inhibited SARS-COV in in-vitro and clinical studies [56], but further studies are required to confirm their effects on SARS-COV-2.

Similarly, darunavir binds to the PLVP protease of the virus, [55] and a study from China demonstrated its inhibitory effect on SARS-COV-2 in vitro [57].

The replication of SARS-COV-2 relies on a chymotrypsin-like protease (3CL pro) to form the RNA replicase-transcriptase complex [58]. The HCV drug danoprevir inhibits this protease, and was tested in conjunction with ritonavir on 11 patients. All of them were discharged with significantly improved symptoms and normal body temperatures within 12 days [59].

Corticosteroids:

Studies show that the use of corticosteroids might accelerate recovery from COVID-19. However, there are no controlled clinical trials that show whether the use of corticosteroids can reduce COVID-19-related death or not [47].

Miscellaneous drugs:

Nitric Oxide has a viricidal effect and was used against SARS-COV in 2004. A randomized clinical trial using nitric oxide on SARS-COV-2 is currently underway and results are to be published soon [60].

Other drugs under investigation include leronlimab which is a humanized monoclonal antibody for the Chemokine Receptor CCR5 and improves immune system response against cytokine release storm that may occur due to COVID-19 [61].

Other drugs such as umifenovir, galidesivir, camrelizumab, rintatolimod and brilacidin are suggested to be tested in clinical trials for COVID-19 treatment [62, 63].

Convalescent plasma possibilities against COVID-19:

Treating patients using plasma from patients who have completely recovered from the virus is a potential option. Using convalescent plasma as therapy for viral infections is not a newfound concept. In fact, it has been used against SARS-COV and recommended by WHO to treat the Ebola virus during the outbreak in 2014 [64].

The efficiency of convalescent plasma in treating viral infections could be explained by its ability to suppress viraema [65]. Multiple articles have discussed and suggested the use of convalescent plasma against SARS-COV-2 [66, 67], and a study on 20 January 2020 was conducted on 5 patients using convalescent plasma and methylprednisolone to treat SARS-COV-2. It showed to reduce the temperature and relieve most symptoms and 3 of the 5 patients were discharged from hospital after 12 days.

However, these results are controversial due to the limited number of patients and the use of methylprednisolone, which may have been the cause of recovery [68].

Further studies are required to test the viability of convalescent plasma as a treatment for COVID-19, so its use on critically ill patients was approved by FDA in March 2020 [69].

Conclusion:

Researches on COVID-19 treatments and preventive measures are rapidly progressing, and it is difficult to keep up with all presumptive treatments. In fact, most of the above-mentioned drugs have not been fully tested and further clinical studies are needed for the final approval. Therefore, due to the urgency of the situation, these drugs were advanced to be used in COVID-19 patients, depending on the encouraging and positive results obtained from different nations and on case to case basis.

On the other hand, researchers mostly tested drugs that had been already used against SARS-COV due to its similarities with SARS-COV-2, along with the other medications that were previously approved for various infections. Nevertheless, developing new drugs, clinical trials, and producing vaccines became a world health goal to be achieved and mandate us deeply to intense, understand and utilize our knowledge about SARS-COV-2 and its clinical manifestations. No vaccine is currently available and the development of one is an urgent matter. In fact, since, COVID-19 evolves continually and there are multiple strains and types of it, the promise to have an effective vaccine in the early stage is a big challenge and may not occur.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223): 497-506.

2. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020;55(3):105924. DOI:10.1016/j.ijantimicag. 2020.105924.

3. Zhang T, He Y, Xu W, Ma A, Yang Y, Xu KF. Clinical trials for the treatment of Coronavirus disease 2019 (COVID-19): A rapid response to urgent need. Sci China Life Sci. 2020;63(5):774-6. DOI:10.1007/s11427-020-1660-2.

4. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7. DOI:10.1002/path.1570.

5. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11(8):875-879. DOI:10.1038/nm1267.

6. Hoffmann M, Kleine-Weber H, Krüger N, Mueller M A, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. BioRxiv. 2020; DOI: 10.1101/2020.01.31.929042.

7. Li F, Li W, Farzan M, Harrison SC. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science.2005; 309(5742): 1864-8.

8. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 2020;63(3):457-60. DOI:10.1007/s11427-020-1637-5.

9. Zeinalian M, Salari-Jazi A, Jannesari A, Khanahmad H. A potential protective role of losartan against coronavirus-induced lung damage. Infect Control Hosp Epidemiol. 2020;41(6):752-3. DOI:10.1017/ice.2020.80.

10. Alam I, Kamau A K, Kulmanov M, Arold ST, Pain AT, Gojobori T, et al. Functional pangenome analysis suggests inhibition of the protein E as a readily available therapy for COVID-2019. BioRxiv. 2020; DOI:10.1101/2020.02.17.952895.

11. Batlle D, Wysocki J, Satchell K. Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? Clinical Science. 2020; 134(5): 543-5. DOI:10.1042/CS20200163.

12. Lei C, Fu W, Qian K, Li T, Zhang S, Ding M, et al. Potent neutralization of 2019 novel coronavirus by recombinant ACE2-Ig. BioRxiv.2020; DOI: 10.1101/2020.02.01.929976.

13. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-80. DOI:10.1016/j.cell.2020.02.052.

14. Chen J, Zhang L, Yang N, Cao M, Tian M, Fu Q, et al. Characterization of the immune roles of cathepsin L in turbot (Scophthalmus maximus L.) mucosal immunity. Fish Shellfish Immunol. 2020; 97: 322-35. DOI: 10.1016/j.fsi.2019.12.005.

15. Zhang J, Ma X, Yu F, Liu J, Zou F, Pan T, et al. Teicoplanin potently blocks the cell entry of 2019-nCoV. BioRxiv. 2020; DOI: 10.1101/2020.02.05.935387.

16. Yang N, Shen HM. Targeting the Endocytic Pathway and Autophagy Process as a Novel Therapeutic Strategy in COVID-19. Int J Biol Sci. 2020;16(10):1724-31. DOI:10.7150/ijbs.45498.

17. Baron SA, Devaux C, Colson P, Raoult D, Rolain JM. Teicoplanin: an alternative drug for the treatment of COVID-19? Int J Antimicrob Agents. 2020; 55; DOI: 10.1016/j.ijantimicag.2020.105944.

18. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents. 2020;55(5):105938. DOI:10.1016/j.ijantimicag.2020.105938.

19. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2:69. DOI:10.1186/1743-422X-2-69.

20. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020;16(3):155-66. DOI:10.1038/s41584-020-0372-x.

21. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother. 2020;75(7):1667-70. DOI:10.1093/jac/dkaa114.

22. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020; 55(4):105932. DOI: 10.1016/j.ijantimicag.2020.105932.

23. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Clin Infect Dis. 2020; 71(15):732-9. DOI:10.1093/cid/ciaa237.

24. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949. DOI:10.1016/j.ijantimicag.2020.105949.

25. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020;14(1):72-3. DOI:10.5582/bst.2020.01047.

26. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269-71. DOI:10.1038/s41422-020-0282-0.

27. Yethindra V. Role of GS-5734 (Remdesivir) in Inhibiting SARS-CoV and MERS-CoV: The Expected Role of GS-5734 (Remdesivir) in COVID-19 (2019-NCoV) - VYTR Hypothesis. Int J Res Pharm Sci. 2020; 11: 1-6. DOI: 10.26452/ijrps.v11iSPL1.1973

28. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020;14(1):58-60. doi:10.5582/ddt.2020.01012.

29. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020. DOI:10.1056/NEJMoa2001191.

30. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. J Korean Med Sci. 2020;35(6):e79. DOI:10.3346/jkms.2020.35.e79.

31. Guo YR, Cao QD, Hong ZS, Tan Y-Y, Chen S-D, Jin H-J, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020;7(1):11. DOI:10.1186/s40779-020-00240-0.

32. Boretti A, Banik BK. Intravenous Vitamin C for reduction of cytokines storm in Acute Respiratory Distress Syndrome. PharmaNutrition. 2020;12:100190. DOI:10.1016/j.phanu.2020.100190.

33. Simonson W. Vitamin C and coronavirus. Geriatr Nurs. 2020;41(3):331-2. DOI:10.1016/j.gerinurse.2020.05.002.

34. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. Lancet Respir Med. 2020;8(5):433-4. DOI:10.1016/S2213-2600(20)30127-2.

35. Wang L, Wang Y, Ye D, Liu Q. Review of the 2019 novel coronavirus (SARS-CoV-2) based on current evidence. Int J Antimicrob Agents. 2020;55(6):105948. DOI:10.1016/j.ijantimicag.2020.105948.

36. Aminnejad R, Salimi A, Saeidi M. Lidocaine during intubation and extubation in patients with coronavirus disease (COVID-19). Can J Anaesth. 2020;67(6):759. DOI:10.1007/s12630-020-01627-2.

37. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395 (10223):497–506. DOI:10.1016S0140–6736(20)30183–5.

38. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020;20(4):400-2. DOI:10.1016/S1473-3099(20)30132-8.

39. Bekerman E, Neveu G, Shulla A, Brannan J, Pu S-Y, Wang S, et al. Anticancer kinase inhibitors impair intracellular viral trafficking and exert broad-spectrum antiviral effects. J Clin Invest. 2017;127(4):1338-52. DOI:10.1172/JCI89857.

40. Pu SY, Xiao F, Schor S, Bekerman E, Zanini F, Barouch-Bentov R, et al. Feasibility and biological rationale of repurposing sunitinib and erlotinib for dengue treatment. Antiviral Res. 2018;155:67-75. DOI:10.1016/j.antiviral.2018.05.001.

41. Sanchez GAM, Reinhardt A, Ramsey S, Wittkowski H, Hashkes PJ, Berkun Y, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J Clin Invest. 2018;128(7):3041-52. DOI:10.1172/JCI98814.

42. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus susceptibility to the antiviral remdesivir (gs-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. mBio. 2018;9(2): e00221–18. DOI:10.1128/mBio.00221-18.

43. González Canga A, Sahagún Prieto AM, Diez Liébana MJ, Fernández Martínez N, Sierra Vega M, García Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans--a mini-review. AAPS J. 2008;10(1):42-6. DOI:10.1208/s12248-007-9000-9.

44. Buonfrate D, Salas-Coronas J, Muñoz J, Trevino Maruri B, Rodari P, Castelli F, et al. Multiple-dose versus single-dose ivermectin for Strongyloides stercoralis infection (Strong Treat 1 to 4): a multicentre, open-label, phase 3, randomised controlled superiority trial. Lancet Infect Dis. 2019;19(11):1181-90. DOI:10.1016/S1473-3099(19)30289-0.

45. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J. 2012;443(3):851-6. DOI:10.1042/BJ20120150.

46. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;178:104787. DOI:10.1016/j.antiviral.2020.104787.

47. Saghazadeh A, Rezaei N. Towards treatment planning of COVID-19: Rationale and hypothesis for the use of multiple immunosuppressive agents: Anti-antibodies, immunoglobulins, and corticosteroids. Int Immunopharmacol. 2020;84:106560. DOI:10.1016/j.intimp.2020.106560.

48. Liu T, Zhang J, Yang Y, Ma H, Li Z, Zhang J, et al. The role of interleukin-6 in monitoring severe case of coronavirus disease 2019. EMBO Mol Med. 2020;12(7):e12421. DOI:10.15252/emmm.202012421.

49. Davies R, Choy E. Clinical experience of IL-6 blockade in rheumatic diseases - implications on IL-6 biology and disease pathogenesis. Semin Immunol. 2014;26(1):97-104. DOI:10.1016/j.smim.2013.12.002.

50. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020;117(20):10970-5. DOI:10.1073/pnas.2005615117.

51. Mazzitelli M, Arrighi E, Serapide F, Chiara Pelle M, Tassone B, Lionello R, et al. Use of subcutaneous tocilizumab in patients with COVID-19 pneumonia. J Med Virol. 2020; DOI:10.1002/jmv.26016.

52. Capra R, De Rossi N, Mattioli F, Romanelli G, Scarpazza C, Pia Sormani M, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med. 2020; DOI:10.1016/j.ejim.2020.05.009.

53. Yao TT, Qian JD, Zhu WY, Wang Y, Wang G-Q. A Systematic Review of Lopinavir Therapy for SARS Coronavirus and MERS Coronavirus-A Possible Reference for Coronavirus Disease-19 Treatment Option. J Med Virol. 2020. DOI: 10.1002/jmv.25729.

54. Su B, Wang Y, Zhou R, Jiang T, Zhang H, Li Z, et al. Efficacy and Tolerability of Lopinavir/Ritonavir- and Efavirenz-Based Initial Antiretroviral Therapy in HIV-1-Infected Patients in a Tertiary Care Hospital in Beijing, China. Front Pharmacol. 2019;10:1472. DOI:10.3389/fphar.2019.01472.

55. Lin S, Shen R, He J, Li X, Guo X. Molecular Modeling Evaluation of the Binding Effect of Ritonavir, Lopinavir and Darunavir to Severe Acute Respiratory Syndrome Coronavirus 2 Proteases. bioRxiv.2020; DOI: 10.1101/2020.01.31.929695.

56. Chu CM, Cheng VC, Hung IF, Wong M M L, Chan K H, Chan K S, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004;59(3):252-6. DOI:10.1136/thorax.2003.012658.

57. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020;14(1):58-60. DOI:10.5582/ddt.2020.01012.

58. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virol. 2020; 94(7):e00127-20. doi: 10.1128/JVI.00127-20.

59. Chen H, Zhang Z, Wang L, Huang Z, Gong F, Li X, et al. First Clinical Study Using HCV Protease Inhibitor Danoprevir to Treat Naive and Experienced COVID-19 Patients. medRxiv. 2020; DOI: 10.1101/2020.03.22.20034041.

60. Lei C, Su B, Dong H, Fakhr BS, Grassi LG, Di Fenza R, et al. Protocol for a randomized controlled trial testing inhaled nitric oxide therapy in spontaneously breathing patients with COVID-19. Preprint. medRxiv. 2020; DOI:10.1101/2020 .03.10.20033522.

61. Miao M, De Clercq E, Li G. Clinical significance of chemokine receptor antagonists. Expert Opin Drug Metab Toxicol. 2020;16(19:11–30. DOI: 10.1080/17425255.2020.1711884.

62. McCreary EK, Pogue JM. Coronavirus Disease 2019 Treatment: A Review of Early and Emerging Options. Open Forum Infect Dis. 2020;7(4). DOI:10.1093/ofid/ofaa105.

63. Sorbera LA, Graul A I, Dulsat C. Taking aim at a fast-moving target: targets to watch for SARS-CoV-2 and COVID-19. Drugs of the Future. 2020; 45(4): 1-6. DOI: 10.1358/dof.2020.45.4.3150676.

64. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng M H L, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis. 2005; 24(1): 44–6. DOI 10.1007/s10096-004-1271-9.

65. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020;20(4):398-400. DOI:10.1016/S1473-3099(20)30141-9.

66. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest. 2020;130(4):1545-8. DOI:10.1172/JCI138003.

67. Shanmugaraj B, Siriwattananon K, Wangkanont K, Phoolcharoen W. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19). Asian Pac J Allergy Immunol. 2020;38(1):10-18. DOI:10.12932/AP-200220-0773.

68. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA. 2020;323(16):1582-9. DOI:10.1001/jama.2020.4783.

69. Tanne JH. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. BMJ. 2020; DOI:10.1136/bmj.m1256.

How to cite this article:

Rim M. Harfouch, Samer Alshaikh, Mohammad Alshimaly, Amany Assaad, Jehan Ahmad, Haya Zoughaibi, Maher Hammadi, Yahya Elshimali. Therapeutic approaches for COVID 19: Challenges and successes. Ann Clin Anal Med 2021;12(2):228-233